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Molecular mechanisms of ovarian follicular development and early embryogenesis

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ABSTRACT

In the mammalian ovary, the dormant primordial follicles are the source of developing follicles and fertilizable ova for the entire reproductive life. In addition, the duration of fertility of a female is determined by the initial size of her pool of primordial follicles and by the rate of its activation and depletion. Menopause (the end of female reproductive life), also known as ovarian senescence occurs when the pool of primordial follicles is exhausted. However, the molecular mechanisms underlying the reproductive aging and menopausal age in females are poorly understood. In this thesis, by generating the oocyte-specific deletion of *Rptor*, *Tsc2* and *Pdk1* in mice, I have thus studied PI3K-mTORC1 signaling in oocytes in physiological development of follicles and early embryogenesis of mice.

We provided *in vivo* evidence that deletion of *Rptor* in oocytes of primordial and further developed follicles leads to the ablation of mTORC1 signaling. However, upon the loss of mTORC1 signaling in oocytes, follicular development and fertility of mice lacking *Rptor* in oocytes were not affected. Interestingly, PI3K signaling was found to be elevated upon the loss of mTORC1 signaling in oocytes, and become essential to maintain normal physiological development of ovarian follicles and fertility of females. Therefore, it indicates that the loss of mTORC1 signaling in oocytes triggers a compensatory activation of the PI3K-Akt signaling that maintains normal ovarian follicular development and fertility.

However, the female mice lacking *Tsc2*, a negative regulator of mTORC1, in oocytes produced at most two litters of normal size and then became infertile in young adulthood. We found that the mTORC1–S6K1–rpS6 signaling is elevated upon the deletion of *Tsc2* in oocytes, leading to the overactivation of pool of primordial follicle in ovaries of mice lacking *Tsc2* in oocytes. Consequently, the ovaries lacking *Tsc2* in oocytes were observed to be completely devoid of follicles, causing POF in early adulthood. Therefore, we identified the *Tsc2* gene as an essential factor in oocytes to preserve the female reproductive lifespan by suppressing the activation of primordial follicles.

Furthermore, we had shown that blockage of maternal PI3K signaling by deletion of *Pdk1* from primary oocytes leads to the arrest of resultant embryos at the two-cell stage, which is most probably a consequence of suppressed EGA and a defective G2/M phase at the two-cell stage. Surprisingly, concurrent loss of maternal *Pten* recovered the impaired Akt activation, rescued the suppressed EGA and two-cell arrest of embryos, and restored the fertility of double-mutant females. We therefore identified the maternal PI3K/Pten–Pdk1–Akt signalling cascade as an indispensable maternal effect factor in triggering EGA and sustaining preimplantation embryogenesis in mice.

In summary, Tsc2/mTORC1 signaling in oocytes is essential for the maintenance of quiescence and the survival of primordial follicles, and thereby controls the reproductive aging and menopausal age in females. Furthermore, the molecular network involved in PI3K/Pten–Pdk1–Akt signalling is crucial for EGA and preimplantation embryogenesis in mice.

Key words: ovary, primordial follicles, Embryogenesis, PI3K-mTORC1 signaling.
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